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John P. Parise
(Print Name)

Date: February 22, 1999

(Signature)

PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application

Binggeli et al — Group: 1613

Serial No. 08/711,339 filed September 6, 1996 — Examiner: R. Ramseur

For: NOVEL PIPERIDINE DERIVATIVES HAVING RENIN INHIBITING ACTIVITY

APPEAL BRIEF

Nutley, New Jersey 07110
February 22, 1999

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

This is an appeal under 35 U.S.C. §134 pursuant to 37 CFR §1.192 from the September 25, 1998 effective final rejection of claims 1-40 and 42-137. This Brief is submitted in triplicate, along with a Request to Charge Deposit Account

No. 08-2525 for any fees in connection with this Appeal. An Oral Hearing is requested.

1. REAL PARTY IN INTEREST

The rights to this application have been assigned to Hoffmann-La Roche Inc., Nutley, New Jersey, U.S.A.

2. RELATED APPEALS AND INTERFERENCES

There are no related appeals or interferences.

3. STATUS OF CLAIMS

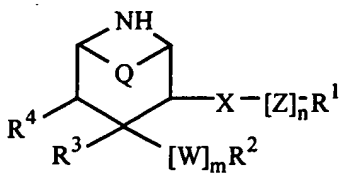
Claims 1-40 and 42-137 are pending in the subject application. According to the Office Action, portions of claims 1-17, 20, 32, 33, 35-39, 42-45, 47, 68-72, 74, 77, 87-90, and all of claims 18, 19, 21-31, 34, 46, 48-67, 73, 75, 76, 79-86, and 91-136, have been withdrawn from further consideration under 37 C.F.R. §1.142(b), and claims 40, 78, and 137 have been objected to as being dependent upon a non-allowed claim. The Patent Office has not rejected any claim *per se*. However, it is appellants' position that the Patent Office has in fact rejected all of the pending claims as a result of a failure to examine appellants' claimed invention. A copy of claims 1-40 and 42-137 as now present in this application is attached hereto as an Appendix.

4. STATUS OF AMENDMENTS

The rejection of claims 1-41 and 43-137 by the Patent Office's refusal to examine appellants' claimed invention was made final in the September 25, 1998 Office Action. Appellants' only amendment, i.e. the Amendment filed on November 7, 1997 correcting a typographical error, has been entered.

5. SUMMARY OF THE INVENTION

The invention relates to compounds of the formula:



I

wherein

R^1 is aryl or heterocyclyl;

R^2 is phenyl, naphthyl, acenaphthyl, cyclohexyl, pyridyl, pyrimidinyl, pyrazinyl, oxo-pyridinyl, diazinyl, triazolyl, thienyl, oxazolyl, oxadiazolyl, thiazolyl, pyrrolyl or furyl, which groups can be substituted by 1-3 halogen, hydroxy, cyano, trifluoromethyl, lower-alkyl, halo-lower-alkyl, hydroxy-lower-alkyl, lower-alkoxy-lower-alkyl, cyano-lower-alkyl, carboxy-lower-alkyl, lower-alkanoyloxy-lower-alkyl, lower-alkoxycarbonyloxy-lower-alkyl, lower-alkoxycarbonyl, or lower-alkoxy groups, or by lower-alkylenedioxy, and/or by a group L^1-T^1-L^2-T^2-L^3-T^3-L^4-T^4-L^5-U;

L^1, L^2, L^3, L^4 and L^5 independently of one another are a bond, C_{1-8}-alkylene, C_{2-8}-alkenylene or C_{2-8}-alkynylene or are absent;

T^1, T^2, T^3 and T^4 independently of one another are

(a) a bond or are absent or are one of the groups

(b) -CH(OH)-

(c) $-CH(OR^6)-$

(d) $-CH(NR^5R^6)-$

(e) -CO-

(f) $-CR^7R^8-$

(g) -O- or $-NR^6-$

(h) $-S(O)_{0-2}-$

(i) $-SO_2NR^6-$

(j) $-NR^6SO_2-$

(k) $-CONR^6-$

(l) $-NR^6CO-$

(m) -O-CO-

(n) -CO-O-

(o) -O-CO-O-

(p) $-O-CO-NR^6-$

(q) $-NR^6-CO-NR^6-$

(r) $-NR^6-CO-O-$

and the bonds emanating from (b), (d), (e) and (g)-(r) join to a C atom of the adjacent group and this C atom is saturated when the bond emanates from a hetero atom, and not more than two groups (b)-(f), three groups (g)-(h) and one group (i)-(r) are present;

R^3 is hydrogen, hydroxy, lower-alkoxy or lower-alkenyloxy; and

R^4 is hydrogen, lower-alkyl, lower-alkenyl, lower-alkoxy, hydroxy-lower-alkyl, lower-alkoxy-lower-alkyl, benzyl, oxo or a group
R^{4a}-Z^1-X^1- in which R^{4a} is
(a) H-
(b) lower-alkyl-
(c) lower-alkenyl-
(d) hydroxy-lower-alkyl-
(e) polyhydroxy-lower-alkyl-
(f) lower-alkyl-O-lower-alkyl-
(g) aryl-
(h) heterocyclyl-
(i) arylalkyl-
(j) heterocyclylalkyl-
(k) aryloxyalkyl-
(l) heterocyclyloxylalkyl-
(m) (R^5R^6)-N-$(CH_2)_{1-3}$-
(n) (R^5R^6)-N-
(o) lower-alkyl-$S(O)_{0-2}$-
(p) aryl-$S(O)_{0-2}$-
(q) heterocyclyl-$S(O)_{0-2}$-
(r) HO-SO_3- or salt thereof
(s) H_2N-C(NH)-NH-
(t) NC-,
and the bonds emanating from (n)-(t) join to a C atom of the adjacent group and this C atom is saturated when the bond emanates from a hetero atom;

Z^1 is

(a) a bond, is absent or is one of the groups

(b) lower-alkylene-

(c) lower-alkenylene-

(d) -O-,-N(R^{11})-,-S(O)$_{0-2}$-

(e) -CO-

(f) -O-CO-

(g) -O-CO-O-

(h) -O-CO-N(R^{11})-,

(i) -N(R^{11})-CO-O-

(j) -CO-N(R^{11})-

(k) -N(R^{11})-CO-

(l) -N(R^{11})-CO-N(R^{11})-

(m) -CH(OR^{9})-,

and the bonds emanating from (d) and (f)-(m) join to a C atom of the adjacent group and this C atom is saturated when the bond emanates from a hetero atom;

X^1 is

(a) a bond, is absent or is one of the groups

(b) -O-

(c) -N(R^{11})-,

(d) -S(O)$_{0-2}$-

(e) -(CH_2)$_{1-3}$-

or R^3 and R^4 together are a bond;

R^5 and R^6 are hydrogen, lower-alkyl, lower-alkenyl, aryl-lower-alkyl or acyl or together with the N atom to which they are attached are a 5- or 6-membered heterocyclic ring which can contain an additional N atom or an O or S atom or a SO or SO_2 group and the additional N atom can be optionally substituted by lower-alkyl;

R^7 and R^8 together with the C atom to which they are attached are a 3-7 membered ring which can contain one or two O or S atoms or SO or SO_2 groups;

R^9 is hydrogen, lower-alkyl, acyl or arylalkyl;

R^{10} is carboxyalkyl, alkoxycarbonylalkyl, alkyl or hydrogen;

R^{11} is hydrogen or lower-alkyl;
U is hydrogen, lower-alkyl, cycloalkyl, cyano, optionally substituted cycloalkyl, aryl or heterocyclyl;

Q is ethylene or is absent;

X is a bond, oxygen, sulphur or a group -CH-R^{11}-, -CHOR^9-, -O-CO, -CO- or C=NOR^{10}-with the bond emanating from an oxygen or sulphur atom joining to a saturated C atom of group Z or to R^1;

W is oxygen or sulphur;

Z is lower-alkylene, lower-alkenylene, hydroxy-lower-alkylidene, -O-, -S-, -O-Alk-, -S-Alk-, -Alk-O- or -Alk-S-, in which Alk is lower alkylene; provided that

a) X is -CH-R^{11}- and either R^2 contains a substituent L^1-T^1-L^2-T^2-L^3-T^3-L^4-T^4-L^5-U or R^4 is a substituent defined above other than hydrogen when Z is -O- or -S-;

b) X is -CH-R^{11}- when Z is -O-Alk- or -S-Alk-; and

c) Z is lower-alkenylene, -Alk-O- or -Alk-S- when X is a bond;

n is 1 or, when X is -O-CO-, 0 or 1; and

m is 0 or 1;

and pharmaceutically usable salts thereof;
with the proviso that said compound is not 4-(4-fluorophenyl)-3-(3,4-methylenedioxybenzyloxy)piperidine or its hydrochloride. These compounds are useful in controlling high blood pressure.

6. ISSUES

Does 35 U.S.C. §121 give the Patent Office the authority to create a "generic concept" inclusive of a species elected by applicant and require applicant to amend a single claim embracing the "generic concept" so as to only encompass the "generic concept" in order for that single claim to be examined and considered on the merits?

7. GROUPING OF CLAIMS

Claims 1-41 and 43-137 are presented for appeal. All claims stand or fall together with respect to the rejection caused by the Patent Office's refusal to examine appellants' claimed invention. Claims 1-17, 20, 32, 33, 35-39, 42-45, 47, 68-72, 74, 77, 87-90 directly read upon the elected species. Claims 18, 19, 21-31, 34, 46, 48-67, 73, 75, 76, 79-86, and 91-136 do not read upon the elected species but should be examined and considered on the merits if the invention of claim 1 is deemed patentable.

8. ARGUMENT

A. Background

In an October 16, 1997 Office Action, the Patent Office issued what was believed by applicants to be an election requirement and mentioned that upon election of a species, "a generic concept inclusive of the elected species will be determined by the Examiner for examination along with the elected species." In their Amendment dated November 7, 1997, applicants elected a single species for examination purposes, i.e. the compound of claim 137, (3R,4S,5S)-3-(1,4-

dimethoxy-naphthalen-2-ylmethoxy)-4-[4-[3-(2-methoxy-benzyloxy)-propoxy]-phenyl]-piperidin-5-ol and stated that applicants "look forward to the species embodied by the compound of claim 137 being found patentable and to a further determination of patentablity for the genus that includes this species, as embodied in claim 1."

In response to the November 7, 1997 Amendment, the Patent Office in its March 23, 1998 Office Action identified a "generic concept" which was created by the Patent Office to encompass applicants' claimed species. In their August 10,1998 Office Action, applicants argued that the Patent Office's position was not supported by the law for the reasons set forth below.

In the September 25, 1998 Final Office Action, the Patent Office made final its restriction requirement that presumably restricts the claimed compounds into two groups: (1) the "generic concept" and (2) all other compounds. However, it in view of the "generic concept" approach it is uncertain whether the second group contains a single or many allegedly independent inventions. In the Final Office Action, the Patent Office made it clear that

> "The issue here is one of restriction. 35 U.S.C. 121 gives the Commissioner the authority to restrict the examination of an application to one invention where two or more inventions are claimed."

In a December 22, 1998 Communication, applicants again argued that the Patent Office's position was not supported by the law for the reasons set forth below.

Applicants petitioned the Commissioner under 37 C.F.R. §1.444 on November 11,1998 requesting withdrawal of the restriction requirement because it does not comply with Patent Office procedure or law. On February 3, 1999, the Commissioner issued a decision denying applicants' Petition. The decision of the Commissioner appears to be based on an analysis related to the judicially created doctrine regarding improper Markush groupings. No rejection of the claims has been made under such a doctrine. Rather, the Patent Office has maintained an intraclaim restriction requirement based on 35 U.S.C. §121.[1] No rejection has been made on the merits.[2]

Applicants note that they previously requested that the Patent Office consider documents A2, A3, B2 and B3 submitted together with Information Disclosure Statements (filed July 16, 1998 and August 10, 1998) and identified on

[1] The February 3, 1999 Petition Decision incorrectly states "applicants did not offer any suggestions as to a proper genus or argue that the genus determined by the examiner was improper except with respect to the entire scope of claim 1." On the contrary, applicants discussed this at a June 24, 1998 interview with the Examiner. Applicants and the Examiner came to no agreement as to this issue.

[2] The phrase "on the merits" includes 35 U.S.C. §100, 101, 102, 103, and 112. See *In re Harnisch*, 206 U.S.P.Q. 300, 304 (CCPA 1980).

Forms 1449. No initialed copies of the Forms 1449 have been received by applicants.

B. Legal Argument

The Board of Patent Appeals and Interferences has jurisdiction to hear this appeal. The claims have been effectively rejected by failure of the Patent Office to examine appellants' claims under the guise of restriction under 35 U.S.C. §121. Such refusal to examine applicants' claims is tantamount to a rejection and appealable. *In re Hass*, 179 USPQ 623 (CCPA 1973) ("*Hass I*").

> "An examiner's adverse action of this nature *is* a rejection, a denial of substantive rights. Review thereof must fall within the jurisdiction of the board. *Hass I* at 627 (emphasis in original text).

The Patent Office pointed out in the Office Action that "[t]he issue here is one of restriction." The restriction requirement was made solely under 35 U.S.C. §121 and not under some other doctrine such as "improper Markush rejections and to MPEP 803.02" (see page 2 of the November 25, 1998 Office Action). Therefore, the issue is straightforward and this matter should proceed as in *In re Hass*, 198 USPQ 335 (CCPA 1978) ("*Hass II*").

It is well-established law that restriction within a single claim cannot be sustained under 35 U.S.C. §121. As is stated in *In re Weber*, 198 U.S.P.Q. 328 (CCPA 1978) at pages 331-332,

> "§121 provides the Commissioner with the authority to promulgate rules designed to *restrict an application* to one of several claimed inventions when those inventions are found to be "independent and distinct." It is not, however, provide a basis for the Examiner acting under the authority of the Commissioner to *reject* a particular *claim* on that same basis." (Emphasis in original text).

In the subject application, the Patent Office made the exact type of restriction expressly forbidden by the CCPA in *In re Weber* (such restriction is tantamount to a rejection). There is no basis under 35 U.S.C. §121 for the Patent Office to make an intraclaim restriction requirement of claim 1 and the subsequent generic claims encompassing the species of claim 137.

Appellants find nothing in 35 U.S.C. §121 that gives the Patent Office legal authority to create a "generic concept" and require applicants to amend a particular claim so as to only claim the subject matter indicated as being allowable, i.e. claim 1 as limited to embrace the generic concept.[3] Applicants have the right under U.S. patent law to claim their invention using the limitations that they regard as essential to delineate the invention, as long as the requirements of 35 U.S.C. §112 are met. See *In re Weber* at 331.

[3] The "generic concept" refers to the subject matter of claim 1 limited to where R^1 is aryl optionally substituted by lower alkyl, lower alkenyl, trifluoromethyl, lower alkoxy, hydroxy-lower alkoxy, alkoxy-alkoxy; R^2 is phenyl or naphthyl each substituted by -O-C_{1-8} alkylene or –O-C_{1-8} alkylene-aryl wherein aryl is as defined for R^1; X is O, S; Z is lower alkylene; Q is absent; m is O (W is absent); R^3 is hydrogen; R^4 is OH.

As in *Hass I*, the claims in the present application are being withdrawn from consideration not only in this application but also prospectively in any subsequent application because of their content. As the Patent Office's "generic concept" is constructed, it would be impossible for applicants to garner in subsequent patent applications the remainder of the claims after the "generic concept" is cleaved out[4], especially with regard to the written description requirement.

If the Patent Office is permitted to create a "generic concept", numerous issues arise as to who is the inventor of the "generic concept"? and does the specification provide a written description of the "generic concept"? Although every species contained within the "generic concept" would be enabled by the specification, the "generic concept" *per se* could lack a written description in the specification as filed. This is the exact situation envisioned in *In re Weber* which states on page 331:

> If, however, a single claim is required to be divided up and presented in several applications, that claim would never be considered on the merits. The totality of the resulting fragmentary claims would not necessarily be the equivalent of the original claim. Further, since the sub-genera would be defined by the examiner rather than the applicant, it is not inconceivable that a number of the fragments would not be described by the specification.

[4] Appellants note that the Patent Office did not provide a number of distinct catagories under into which the compounds of claim 1 could be divided, but rather, created a "generic concept".

Allowing the Patent Office to proceed via a "generic concept" approach would be a disservice to all patent applicants and is not supported by the law. It is appellants' position that the Patent Office must either allow or reject a claim that reads upon an elected species.

In view of the above, appellants request that the subject application be remanded to the Examiner with the instruction to consider on the merits the entirety of claims 1-17, 20, 32, 33, 35-39, 42-45, 47, 68-72, 74, 77, 87-90, and if claim 1 is deemed patentable, then to consider on the merits claims 18, 19, 21-31, 34, 46, 48-67, 73, 75, 76, 79-86, and 91-136.

Respectfully submitted,

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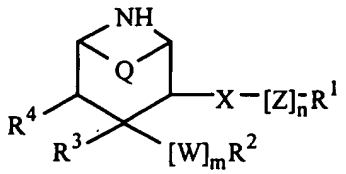
Appellants, therefore, could not predict the number of divisional applications that are being requested by the Patent Office.

9. APPENDIX

1. A compound of the formula:



I

wherein

R^1 is aryl or heterocyclyl;

R^2 is phenyl, naphthyl, acenaphthyl, cyclohexyl, pyridyl, pyrimidinyl, pyrazinyl, oxo-pyridinyl, diazinyl, triazolyl, thienyl, oxazolyl, oxadiazolyl, thiazolyl, pyrrolyl or furyl, which groups can be substituted by 1-3 halogen, hydroxy, cyano, trifluoromethyl, lower-alkyl, halo-lower-alkyl, hydroxy-lower-alkyl, lower-alkoxy-lower-alkyl, cyano-lower-alkyl, carboxy-lower-alkyl, lower-alkanoyloxy-lower-alkyl, lower-alkoxy-carbonyloxy-lower-alkyl, lower-alkoxycarbonyl, or lower-alkoxy groups, or by lower-alkylenedioxy, and/or by a group L^1-T^1-L^2-T^2-L^3-T^3-L^4-T^4-L^5-U;

L^1, L^2, L^3, L^4 and L^5 independently of one another are a bond, C_{1-8}-alkylene, C_{2-8}-alkenylene or C_{2-8}-alkynylene or are absent;

T^1, T^2, T^3 and T^4 independently of one another are

(a) a bond or are absent or are one of the groups

(b) -CH(OH)-

(c) -CH(OR^6)-

(d) -CH(NR^5R^6)-

(e) -CO-

(f) $-CR^7R^8-$

(g) -O- or $-NR^6-$

(h) $-S(O)_{0-2}-$

(i) $-SO_2NR^6-$

(j) $-NR^6SO_2-$

(k) $-CONR^6-$

(l) $-NR^6CO-$

(m) -O-CO-

(n) -CO-O-

(o) -O-CO-O-

(p) $-O-CO-NR^6-$

(q) $-NR^6-CO-NR^6-$

(r) $-NR^6-CO-O-$

and the bonds emanating from (b), (d), (e) and (g)-(r) join to a C atom of the adjacent group and this C atom is saturated when the bond emanates from a hetero atom, and not more than two groups (b)-(f), three groups (g)-(h) and one group (i)-(r) are present;

R^3 is hydrogen, hydroxy, lower-alkoxy or lower-alkenyloxy; and

R^4 is hydrogen, lower-alkyl, lower-alkenyl, lower-alkoxy, hydroxy-lower-alkyl, lower-alkoxy-lower-alkyl, benzyl, oxo or a group

$R^{4a}-Z^1-X^1-$ in which R^{4a} is

(a) H-

(b) lower-alkyl-

(c) lower-alkenyl-

(d) hydroxy-lower-alkyl-

(e) polyhydroxy-lower-alkyl-

(f) lower-alkyl-O-lower-alkyl-

(g) aryl-

(h) heterocyclyl-

(i) arylalkyl-

(j) heterocyclylalkyl-

(k) aryloxyalkyl-

(l) heterocyclyloxylalkyl-

(m) (R^5R^6)-N-$(CH_2)_{1-3}$-

(n) (R^5R^6)-N-

(o) lower-alkyl-$S(O)_{0-2}$-

(p) aryl-$S(O)_{0-2}$-

(q) heterocyclyl-$S(O)_{0-2}$-

(r) HO-SO_3- or salt thereof

(s) H_2N-C(NH)-NH-

(t) NC-,

and the bonds emanating from (n)-(t) join to a C atom of the adjacent group and this C atom is saturated when the bond emanates from a hetero atom;

Z^1 is

(a) a bond, is absent or is one of the groups

(b) lower-alkylene-

(c) lower-alkenylene-

(d) -O-,-N(R^{11})-,-$S(O)_{0-2}$-

(e) -CO-

(f) -O-CO-

(g) -O-CO-O-

(h) -O-CO-N(R^{11})-,

(i) -N(R^{11})-CO-O-

(j) -CO-N(R^{11})-

(k) -N(R^{11})-CO-

(l) -N(R^{11})-CO-N(R^{11})-

(m) -CH(OR^{9})-,

and the bonds emanating from (d) and (f)-(m) join to a C atom of the adjacent group and this C atom is saturated when the bond emanates from a hetero atom;

X^1 is

(a) a bond, is absent or is one of the groups

(b) -O-

(c) -N(R^{11})-,

(d) -$S(O)_{0-2}$-

(e) -$(CH_2)_{1-3}$-

or R^3 and R^4 together are a bond;

R^5 and R^6 are hydrogen, lower-alkyl, lower-alkenyl, aryl-lower-alkyl or acyl or together with the N atom to which they are attached are a 5- or 6-membered heterocyclic ring which can contain an additional N atom or an O or S atom or a SO or SO_2 group and the additional N atom can be optionally substituted by lower-alkyl;

R^7 and R^8 together with the C atom to which they are attached are a 3-7 membered ring which can contain one or two O or S atoms or SO or SO_2 groups;

R^9 is hydrogen, lower-alkyl, acyl or arylalkyl;

R^{10} is carboxyalkyl, alkoxycarbonylalkyl, alkyl or hydrogen;

R^{11} is hydrogen or lower-alkyl;
U is hydrogen, lower-alkyl, cycloalkyl, cyano, optionally substituted cycloalkyl, aryl or heterocyclyl;

Q is ethylene or is absent;

X is a bond, oxygen, sulphur or a group -CH-R^{11}-, -CHOR^9-, -O-CO, -CO- or C=NOR^{10}-with the bond emanating from an oxygen or sulphur atom joining to a saturated C atom of group Z or to R^1;

W is oxygen or sulphur;

Z is lower-alkylene, lower-alkenylene, hydroxy-lower-alkylidene, -O-, -S-, -O-Alk-, -S-Alk-, -Alk-O- or -Alk-S-, in which Alk is lower alkylene; provided that

a) X is -CH-R^{11}- and either R^2 contains a substituent L^1-T^1-L^2-T^2-L^3-T^3-L^4-T^4-L^5-U or R^4 is a substituent defined above other than hydrogen when Z is -O- or -S-;

b) X is -CH-R^{11}- when Z is -O-Alk- or -S-Alk-; and

c) Z is lower-alkenylene, -Alk-O- or -Alk-S- when X is a bond;

n is 1 or, when X is -O-CO-, 0 or 1; and

m is 0 or 1;

and pharmaceutically usable salts thereof;

with the proviso that said compound is not 4-(4-fluorophenyl)-3-(3,4-methylenedioxybenzyloxy)piperidine or its hydrochloride.

2. The compound of claim 1 wherein:

R^2 is unsubstituted phenyl, cyclohexyl, naphthyl or acenaphthyl, or is phenyl or cyclohexyl substituted by halogen, hydroxy, cyano, trifluoromethyl, lower-alkyl, halo-lower-alkyl, hydroxy-lower-alkyl, lower-alkoxy-lower-alkyl, cyano-lower-alkyl, carboxy-lower-alkyl, lower-alkanoyloxy-lower-alkyl, lower-alkoxycarbonyloxy-lower-alkyl, lower-alkoxycarbonyl, lower-alkoxy, lower-alkylenedioxy or by said group L^1-T^1-L^2-T^2-L^3-T^3-L^4-T^4-L^5-U wherein:

T^1, T^2, T^3 and T^4 independently of one another are:

(a) a bond or are absent or are:

(b) -CH(OH)-

(c) $-CH(OR^6)-$

(d) $-CH(NR^5R^6)-$

(e) -CO-

(f) $-CR^7R^8-$

(g) -O- or $-NR^6-$,

(h) $-S(O)_{0-2}-$

(i) $-SO_2NR^6-$

(j) $-NR^6SO_2-$

(k) $-CONR^6-$

(l) $-NR^6CO-$

(m) -O-CO-

(n) -CO-O-

(o) -O-CO-O-

(p) -O-CO-NR^6-,

with the bonds emanating from (b), (d), (e) and (g)-(p) joining to a carbon atom of the adjacent group and said carbon atom being saturated when the bond emanates from a hetero atom, and not more than two groups (b)-(f), three groups (g)-(h) and one group (i)-(p) being present;

R^3 is hydrogen, hydroxy, lower-alkoxy or lower-alkenyloxy;

R^4 is hydrogen, lower-alkyl, lower-alkenyl, lower-alkoxy, hydroxy-lower-alkyl, lower-alkoxy-lower-alkyl or benzyl;

R^5 and R^6 are hydrogen, lower-alkyl or acyl or together with the nitrogen atom to which they are attached are a 5- or 6-membered heterocyclic ring which can contain a second nitrogen atom or an oxygen or sulfur atom;

R^7 and R^8 together with the carbon atom to which they are attached are a 3-7 membered ring which can contain one or two oxygen or sulphur atoms;

U is hydrogen, lower-alkyl, cycloalkyl, cyano, aryl or heterocyclyl;

X is oxygen, sulphur or a group -CH_2-, -CHOR^9- or -OCO- and R^9 is hydrogen, lower-alkyl, acyl or arylalkyl;

W is absent, or W is oxygen or sulphur or is absent when R^3 is hydrogen; and

Z is lower-alkylene or is absent.

3. The compound of claim 2 wherein:

R^1 is phenyl unsubstituted or substituted by lower-alkyl, lower-alkenyl, lower-alkoxy, lower-alkylthio, halogen, hydroxy, hydroxy-lower-alkoxy, lower-alkoxy-lower-alkoxy, lower-alkylsulphinyl, lower-alkylsulphonyl, cyano, trifluoromethyl, trifluoromethoxy, carboxy, cyclobutylmethoxy-lower-alkyl, lower-alkylenedioxy, phenyl, phenoxy, lower-alkoxycarbonylphenyl, hydroxy-lower-alkylphenyl, 2,3-dihydroxy-propylaminocarbonylphenyl, benzyloxy, benzoyl, pyridyl-lower-alkoxy-lower-alkyl or nicotinoylamino-lower-alkyl; or

R^1 is naphthyl, naphthyl substituted by hydroxy, oxo, lower-alkoxy, lower-alkenyloxy, lower-alkoxy-lower-alkoxy, di-lower-alkylamino, 2,3-dihydroxypropoxy, 2,3-dihydroxy-propoxy-lower-alkoxy, 2,3-dimethoxypropoxy, lower-alkoxycarbonyl-lower-alkoxy, carbamoyl-lower-alkoxy, methoxybenzyloxy, hydroxybenzyloxy, phenethyloxy, methylenedioxybenzyloxy, dioxolanyl-lower-alkoxy, cyclopropyl-lower-alkoxy, hydroxy-lower-alkoxy, carbamoyloxy-lower-alkoxy, pyridyl-carbamoyloxy-lower-alkoxy, morpholino-lower-alkoxy, 3-morpholino-2-hydroxypropoxy, N-methyl-piperazino-N-lower-alkoxy, benzoyloxy-lower-alkoxy or picolyloxy; or

R^1 is tetrahydronaphthyl or methyl-substituted tetrahydronaphthyl, or indanyl; or

R^1 is pyridyl, benzimidazolyl, di-lower-alkoxypyrimidinyl, 2- or 5-benzo[b]thienyl, 6- or 7-quinolyl, 6- or 7-isoquinolyl, 6- or 7-tetrahydroquinolyl, 6- or 7-tetrahydro-isoquinolinyl, 6-quinoxalinyl, 6- or 7-quinazolinyl, or R^1 is 6- or 7-quinolyl, 6- or 7-isoquinolyl, 6- or 7-tetrahydroquinolyl, 6- or 7-tetrahydroisoquinolyl, 6-quinoxalinyl, or 6- or 7-quinazolinyl substituted by hydroxy, oxo, lower-alkoxy, lower-alkenyloxy, lower-alkoxy-lower-alkoxy, di-lower-alkylamino, 2,3-dihydroxypropoxy, 2,3-dihydroxypropoxy-lower-alkoxy, 2,3-dimethoxypropoxy, lower-alkoxycarbonyl-lower-

alkoxy, carbamoyl-lower-alkoxy, methoxybenzyloxy, hydroxybenzyloxy, phenethyloxy, methylenedioxybenzyloxy, dioxolanyl-lower-alkoxy, cyclopropyl-lower-alkoxy, hydroxy-lower-alkoxy, carbamoyloxy-lower-alkoxy, pyridyl-carbamoyloxy-lower-alkoxy, morpholino-lower-alkoxy, 3-morpholino-2-hydroxypropoxy, N-methyl-piperazino-N-lower-alkoxy, benzoyloxy-lower-alkoxy or picolyloxy;

R^2 is unsubstituted phenyl or phenyl substituted by halogen, hydroxy, cyano, trifluoromethyl, lower-alkyl, halo-lower-alkyl, hydroxy-lower-alkyl, lower-alkoxy-lower-alkyl, cyano-lower-alkyl, carboxy-lower-alkyl, lower-alkanoyloxy-lower-alkyl, lower-alkoxycarbonyloxy-lower-alkyl, lower-alkoxycarbonyl, lower-alkoxy or lower-alkylenedioxy; or

R^2 is phenyl substituted by a group:

L^1-T^1-L^2-T^2-L^3-T^3-L^4-T^4-L^5-U in which L^1 and L^2 are absent or are C_{1-8}-alkylene and L^3 is absent; and

U is hydrogen, lower-alkyl, cyclo-lower-alkyl, naphthyl, pyridyl, thienyl, pyrazinyl, triazolyl, imidazolyl, phenyl-oxadiazolyl, thienyl-oxadiazolyl, furyl-oxadiazolyl, phenyl-oxazolyl, benzthiazolyl, furyl, pyrimidinyl, nitrobenzthiazolyl, phenyltetrazolyl, morpholinyl, phenyl unsubstituted or substituted by lower-alkyl, lower-alkoxy, lower-alkylthio, lower-alkylsulphinyl, lower-alkylenedioxy, halogen, benzoyl-lower-alkyl, halo-lower-alkyl, lower-alkanoyloxy or hydroxy; or

R^2 is cyclohexyl or benzoyloxycyclohexyl; or

R^2 is naphthyl, tetrahydronaphthyl or acenaphthyl

R^2 is pyridyl or oxopyridyl or pyridyl or oxopyridyl substituted by 3H-2-thioxo-benzthiazolyl, lower-alkoxyphenyl-lower-alkoxy-lower-alkoxy, phenyl-lower-alkoxy-lower-alkoxy, phenyl-lower-alkyl, phenoxy-lower-alkyl or phenyl-lower-alkoxy-lower-alkyl; or

R^2 is pyrimidinyl or pyrimidinyl substituted by benzodioxanyl-lower-alkoxy, biphenylyloxy, cyclohexyl-lower-alkoxy, cyclohexyloxy-lower-alkoxy, halophenyl-lower-alkoxy, halophenyl-oxadiazolyl-lower-alkoxy, indanyl-lower-alkoxy, naphthyl-lower-alkoxy, N-lower-alkyl-phenyl-lower-alkoxy-lower-alkylamino, lower-alkythio, lower-alkoxy, lower-alkoxyphenyl-lower-alkoxy-lower-alkoxy, lower-alkoxyphenyl-lower-alkylamino, lower-alkylpyridyl-lower-alkoxy, phenyl-lower-alkoxy-lower-alkoxy, phenyl-lower-alkoxy-lower-alkylthio, phenyl-lower-alkoxy-lower-alkylamino, phenyl-lower-alkenoxy, phenoxy-phenyl-lower-alkoxy, phenoxy-phenoxy, phenyl-lower-alkynyloxy, phenyl-lower-alkoxy-lower-alkoxy, phenylthio-lower-alkoxy, phenyl-oxazolyl-lower-alkoxy, phenyl-lower-alkynyloxy, phenyl-lower-alkenyloxy, phenyl-lower-alkylamino or phenyl-pyridyl-lower-alkylamino; or

R^2 is halobenzoyl-lower-alkyl-triazolyl, phenyl-lower-alkoxy-lower-alkyl-triazolyl or phenyl-lower-alkoxy-lower-alkoxy-triazolyl;

R^4 is

2-oxo-lower-imidazolidin-1-yl-lower-alkyl,
4-hydroxy-piperazin-1-yl-lower-alkoxy,
4-hydroxy-piperazin-1-yl-lower-alkoxy-lower-alkyl,
4-methyl-piperazin-1-yl-lower-alkoxy,
4-methyl-piperazin-1-yl-lower-alkoxy-lower-alkyl,
4-methyl-piperazin-1-yl-lower-alkyl-carbamoyloxy-lower-alkyl,
1,2,4-triazolyl-lower-alkyl,

amino,

amino-lower-alkyl,

amino-lower-alkyl-amino

amino-lower-alkyl-amino-lower-alkyl,

amino-lower-alkyl-oxy

amino-lower-alkyl-oxy-lower-alkyl,

aminocarbonyloxy-lower-alkyl,

benzyloxy or benzyloxy substituted by lower-alkyl, lower-alkenyl, lower-alkoxy, trifluoromethoxy, lower-alkylthio, hydroxy or halogen,

benzyloxy-lower-alkyl or benzyloxy-lower-alkyl substituted by lower-alkyl, lower-alkenyl, lower-alkoxy or halogen,

carbamoyloxy-lower-alkyl,

cyano-lower-alkyl,

di-lower-alkyl-amino,

di-lower-alkyl-amino-lower-alkyl,

di-lower-alkyl-amino-lower-alkyl-(N-lower-alkyl)-amino-lower-alkyl,

di-lower-alkyl-amino-lower-alkyl-amino

di-lower-alkyl-amino-lower-alkyl-amino-lower-alkyl,

di-lower-alkyl-amino-lower-alkyl-oxy

di-lower-alkyl-amino-lower-alkyl-oxy-lower-alkyl,

dihydroxy-lower-alkoxy,

dihydroxy-lower-alkoxy-lower-alkyl

dihydroxy-lower-alkyl-amino,

dihydroxy-lower-alkyl-amino-lower-alkyl

guanidinyl-lower-alkoxy-lower-alkyl,

guanidinyl-lower-alkyl,

hydroxy,

hydroxy-lower-alkyl,

sulphooxy-lower-alkyl,

hydroxy-lower-alkyl-oxy,

hydroxy-lower-alkyl-oxy-lower-alkyl,

morpholin-4-yl-lower-alkoxy,

morpholin-4-yl-lower-alkoxy-lower-alkyl,

morpholin-4-yl-lower-alkyl-carbamoyloxy-lower-alkyl,

naphthyl-alkoxy or naphthyl-alkoxy substituted by lower-alkoxy,

lower-alkoxy,

lower-alkoxy-lower-alkoxy

lower-alkoxy-lower-alkoxy-lower-alkyl,

lower-alkoxy-lower-alkyl,

lower-alkyl,

lower-alkylsulphonylamino-lower-alkyl,

phenoxy-lower-alkyl or phenoxy-lower-alkyl substiuted by lower-alkyl,

lower-alkoxy,

phenyl-thio-lower-alkyl or phenyl-thio-lower-alkyl substituted by lower-alkyl, lower-alkoxy,

piperazin-4-yl-lower-alkoxy,

piperazin-4-yl-lower-alkoxy-lower-alkyl,

piperidin-1-yl-lower-alkyl-carbamoyloxy-lower-alkyl,

piperidin-4-yl-lower-alkoxy,

piperidin-4-yl-lower-alkoxy-lower-alkyl,

pyridyl-lower-alkyl-oxy,

pyridyl-lower-alkyl-oxy-alkyl,

pyridylthio-lower-alkyl,

pyrimidinyloxy-lower-alkyl or pyrimidinyloxy-lower-alkyl substituted by lower-alkoxy,

tetrazolyl-lower-alkyl,

trifluoromethylsulphonylamino-lower-alkyl or

hydrogen.

4. The compound of claim 3 wherein R^2 is phenyl or phenyl substituted by:

2-benzothiazolyl-thio-lower-alkyl,

2-benzyloxy-3-methoxypropoxy,

2-benzoyloxy-3-methoxypropoxy,

2,3-dihydroxypropoxy,

2-hydroxy-3-benzylamino-propoxy,

2-hydroxy-3-phenoxypropoxy,

2-hydroxy-3-phenylthiopropoxy,

2-methoxy-3-phenoxypropoxy,

2-methoxy-3-benzyloxypropoxy,

2-methyl-3-fluoro-phenylbutyryloxy-lower-alkoxy,

2-lower-alkenyloxy-4-phenylbutyl,

3,4,5-trimethoxyphenyl-oxadiazolyl-lower-alkoxy,

6-nitro-2-benzothiazolyl-thio-lower-alkyl,

benzamido-lower-alkoxy,

benzamido-lower-alkyl,

benzoyl-lower-alkoxy and ketals thereof,

benzoyl-lower-alkyl and ketals thereof,

benzoyl-lower-alkyl-aminocarbonyl-lower-alkyl,

benzoyl-lower-alkoxycarbonyl-lower-alkyl,

benzoyl-lower-alkylaminocarbonyl,

benzoyloxy,

benzoyloxy-lower-alkyl-benzoyloxy-lower-alkoxy,

benzoyloxy-lower-alkoxy,

benzoyloxy-lower-alkyl,

benzthiazolylthio-lower-alkoxy,

benzthiazolylthio-lower-alkyl,

benzylcarbamoyl-lower-alkoxy,

benzyloxy-lower alkylcarbonyloxy-lower-alkyl,

benzyloxy-lower-alkoxy,

benzylthio-lower-alkoxy,

carbamoyloxy-lower-alkoxy,

carbamoyloxy-lower-alkyl,

carboxy-lower-alkoxy,

carboxy-lower-alkyl,

cyano,

cyano-lower-alkoxy,

cyano-lower-alkyl,

cyanophenyl-lower-alkoxy,

cyclohexylcarbonyloxy-lower-alkyl,

cyclopropylcarbonyloxy-lower-alkyl,

cyclopropyloxy-benzyloxy-lower-alkoxy,

dioxolanyl-lower-alkoxy,

furyl-oxadiazolyl-lower-alkoxy,

furoyloxy-lower-alkoxy,

halo-phenoxy-lower-alkyl,

halobenzoyl-lower-alkoxy,

halobenzoyloxy-lower-alkyl,

halobenzoyloxy-lower-alkoxy,

halobenzyloxy-lower-alkoxy,

halogen,

halogen-lower-alkyl,

halophenoxy,

halophenyl-oxadiazolyl-lower-alkoxy,

hydroxy,

hydroxy-benzoyloxy-lower-alkyl,

hydroxy-benzyloxy-lower-alkoxy,

hydroxy-lower-alkoxy,

hydroxy-lower-alkyl,

imidazolylcarbonyloxy-lower-alkyl,

methoxybenzoyl-lower-alkyl,

methoxybenzyloxy-lower-alkoxy,

methylenedioxybenzoyl-lower-alkoxy,

morpholino-lower-alkoxy,

morpholinocarbonyloxy-lower-alkoxy,

morpholinocarbonyloxy-lower-alkyl,

N-methylaminophenyl-carbonyloxy-lower-alkyl,

N-methyl-benzylamino-lower-alkoxy,

N-methylpyrrolylcarbonyloxy-lower-alkoxy,

N-lower-alkylbenzamido-lower-alkyl,

naphthyl-lower-alkoxy,

nicotinoyloxy-lower-alkoxy,

nicotinoyloxy-lower-alkyl,

lower-alkanoylbenzoyloxy-lower-alkyl,

lower-alkanoyloxy-lower-alkoxy

lower-alkanoyloxy-lower-alkyl,

lower-alkenyl-benzyloxy-lower-alkoxy,

lower-alkenyloxy,

lower-alkenyloxy-benzyloxy-lower-alkoxy,

lower-alkoxy,

lower-alkoxy-benzoyloxy-lower-alkyl,

lower-alkoxy-carbonyl,

lower-alkoxy-lower-alkyl,

lower-alkoxybenzoylamino-lower-alkyl,

lower-alkoxybenzylcarbonyloxy-lower-alkyl,

lower-alkoxy-benzyloxy-lower-alkoxy,

lower-alkoxy-benzylthio-lower-alkoxy,

lower-alkoxycarbonyl,

lower-alkoxycarbonyl-lower-alkoxy,

lower-alkoxycarbonyl-lower-alkyl,

lower-alkoxyphenyl-oxadiazolyl-lower-alkoxy,

lower-alkyl,

lower-alkylbenzyloxy-lower-alkoxy,

lower-alkylenedioxy,

lower-alkylenedioxybenzyloxy-lower-alkoxy,

lower-alkylsulphonylbenzoyl-lower-alkoxy,

lower-alkylthiobenzoyloxy-lower-alkoxy,

lower-alkylthio-benzyloxy-lower-alkoxy,

benzoyloxybenzyl-lower-alkoxy,

hydroxybenzyl-lower-alkoxy,

lower-alkoxybenzyl-lower-alkoxy,

lower-alkoxybenzylcarbonyloxy-alkoxy,

phenoxy-benzyloxy-lower-alkoxy,

phenoxycarbonyl-lower-alkyl,

phenoxy-lower-alkenyloxy,

phenoxy-lower-alkynyloxy,

phenyl-lower-alkanoylamino-lower-alkyl,

phenyl-lower-alkenyloxy,

phenyl-lower-alkoxy,

phenoxy-lower-alkyl,

phenyl-lower-alkylaminocarbonyl,

phenoxy-lower-alkylcarbonyl-lower-alkoxy,

phenyl-lower-alkylaminocarbonyl-lower-alkyl,

phenylaminocarbonyloxy-lower-alkoxy,

phenylaminocarbonyloxy-lower-alkyl,

phenyl-hydroxy-lower-alkyl,

phenyl-oxadiazolyl-lower-alkoxy

phenyl-oxadiazolyl-lower-alkoxy,

phenyl-oxadiazolyl-lower-alkyl,

phenyl-oxazolyl-lower-alkoxy,

phenyloxy-lower-alkoxy,

phenylsulphamoyl-lower-alkyl,

phenylsulphinyl-lower-alkyl,

phenylsulphonyl-lower-alkoxy,

phenylsulphonyl-lower-alkyl,

phenyltetrazolyl-thio-lower-alkyl,

phenylthio-lower-alkoxy,

phenylthio-lower-alkyl,

pyrazinylcarbonyloxy-lower-alkyl,

pyridylaminocarbonyloxy-lower-alkoxy

pyridylaminocarbonyloxy-lower-alkyl,

pyridylcarbamoyloxy,

pyridyl-lower-alkoxy-lower-alkoxy,

pyridyl-lower-alkoxy-lower-alkyl,

pyridyl-oxadiazolyl-lower-alkoxy,

pyridylthio-lower-alkyl,

pyrimidinyloxy-lower-alkoxy,

pyrimidinylthio-lower-alkyl,

thenoyloxy-lower-alkoxy,

thenoyloxy-lower-alkyl,

thienyl-oxadiazolyl-lower-alkoxy,

triazolyl-lower-alkoxy,

trifluoromethylbenzyloxy-lower-alkoxy or

trifluoromethyl.

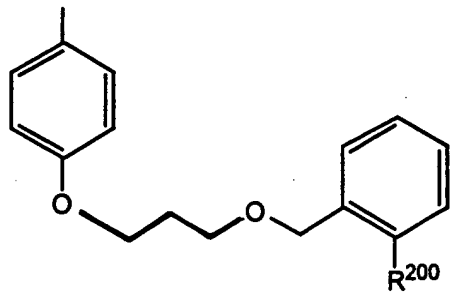
5. The compound of claim 1 wherein R^3 is hydrogen, m is 0 and R^2 is phenyl, pyridyl, pyrimidinyl, pyrazinyl or triazolyl which are unsubstituted or para-substituted, Q is absent, X is oxygen, -CO- or -CHOR^9- wherein R^9 is acetyl, n is 1 and Z is lower alkylene.

6. The compound of claim 5 wherein X is oxygen, Z is methylene, and R^1 is naphthyl which is unsubstituted or substituted.

7. The compound of claim 6 wherein R^1 is napthyl which is unsubstituted or substituted by lower alkoxy, hydroxy, benzyloxy wherein said benzene ring is substituted by methoxy or is unsubstituted, morpholino-lower-alkoxy, piperazino-lower alkoxy wherein the second nitrogen atom is substituted by methyl or is unsubstituted, dihyroxypropoxy, ethoxy dihydroxypropoxy, dihydroxypropoxy-lower alkyl, hydroxypropoxy-lower alkyl, hydroxyethoxy-lower alkyl, or lower alkyl di-lower alkyl amino.

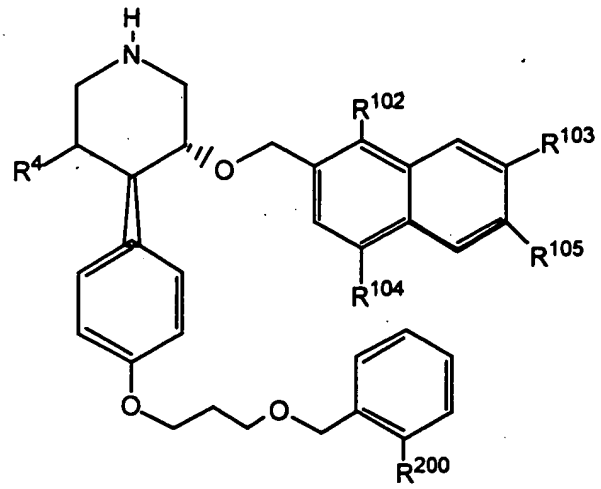
8. The compound of claim 7 wherein R^2 is para-substituted phenyl.

9. The compound of claim 8 wherein R^2 is a group of the formula:



wherein R^{200} is hydrogen or lower alkoxy.

10. The compound of claim 9 having the formula:



wherein R^4 is as in claim 1; R^{102}, R^{103}, R^{104} and R^{105} are independently hydrogen, hydroxy, lower alkoxy, hydroxy lower alkoxy, methyl N,N-dimethyl amine, 2,3-dihyroxypropoxy, 2,3-dihyroxypropoxy-lower alkyl, 2,3-dihyroxypropoxy-lower alkoxy, N-methyl piperazino-N-lower alkoxy, morpholino-lower-alkoxy, benzyloxy, methoxybenzyloxy; and R^{200} is as in claim 9.

11. The compound of claim 10 wherein R^4 is hydrogen.

12. The compound of claim 11 wherein two of R^{102}, R^{103}, R^{104} and R^{105} are hydrogen.

13. The compound of claim 12 wherein R^{103} and R^{105} are hydrogen.

14. The compound of claim 13 wherein R^{102} and R^{104} are methoxy.

15. The compound of claim 14 wherein said compound is (3R,4R)-3-(1,4-dimethoxy-naphthalen-2-ylmethoxy)-4-[4-[3-(2-methoxy-benzyloxy)-propoxy]-phenyl]-piperidine.

16. The compound of claim 12 wherein three of R^{102}, R^{103}, R^{104} and R^{105} are hydrogen.

17. The compound of claim 16 wherein R^{102}, R^{103} and R^{104} are hydrogen.

18. The compound of claim 17 wherein said compound is (3R,4R)-4-[4-(3-benzyloxy-propoxy)-phenyl]-3-[6-[(R)-2,3-dihydroxy-propoxymethyl]-naphthalen-2-ylmethoxy]-piperidine.

19. The compound of claim 17 wherein said compound is (3R,4R)-4-[4-(3-benzyloxy-propoxy)-phenyl]-3-[6-[(S)-2,3-dihydroxy-propoxymethyl]-naphthalen-2-ylmethoxy]-piperidine.

20. The compound of claim 16 wherein R^{102}, R^{104} and R^{105} are hydrogen.

21. The compound of claim 20 wherein said compound is 4-[2-[7-[(3R,4R)-4-[4-(3-benzyloxy-propoxy)-phenyl]-piperidin-3-yloxymethyl]-naphthalen-2-yloxy]-ethyl]-morpholine.

22. The compound of claim 20 wherein said compound is (R)-3-[7-[(3R,4R)-4-[4-(3-benzyloxy-propoxy)-phenyl]-piperidin-3-yloxymethyl]-naphthalen-2-yloxy]-propane-1,2-diol.

23. The compound of claim 20 wherein said compound is (S)-3-[7-[(3R,4R)-4-[4-(3-benzyloxy-propoxy)-phenyl]-piperidin-3-yloxymethyl]-naphthalen-2-yloxy]-propane-1,2-diol.

24. The compound of claim 20 wherein said compound is 1-[2-[7-[(3R,4R)-4-[4-(3-benzyloxy-propoxy)-phenyl]-piperidin-3-yloxymethyl]-naphthalen-2-yloxy]-ethyl]-4-methyl-piperazine.

25. The compound of claim 20 wherein said compound is 1-[2-[7-[(3R,4R)-4-[4-[3-(2-methoxy-benzyloxy)-propoxy]-piperidin-3-yloxymethyl]-naphthalin-2-yloxy]-ethyl]-4-methyl-piperazine.

26. The compound of claim 20 wherein said compound is (R)-3-[2-[7-[(3R,4R)-4-[4-(3-benzyloxy-propoxy)-phenyl]-piperidin-3-yloxymethyl]-naphthalen-2-yloxy]-ethoxy]-propane-1,2-diol.

27. The compound of claim 20 wherein said compound is (S)-3-[2-[7-[(3R,4R)-4-[4-(3-benzyloxy-propoxy)-phenyl]-piperidin-3-yloxymethyl]-naphthalen-2-yloxy]-ethoxy]-propane-1,2-diol.

28. The compound of claim 20 wherein said compound is (3R,4R)-4-[4-(3-benzyloxy-propoxy)-phenyl]-3-[7-[(R)-2,3-dihydroxy-propoxymethyl]-naphthalen-2-ylmethoxy]-piperidine.

29. The compound of claim 20 wherein said compound is (3R,4R)-4-[4-(3-benzyloxy-propoxy)-phenyl]-3-[7-[(S)-2,3-dihydroxy-propoxymethyl]-naphthalen-2-ylmethoxy]-piperidine.

30. The compound of claim 20 wherein said compound is 2-(7-{(3R,4R)-4-[4-(3-benzyloxy-propoxy)-phenyl]-piperidin-3-yloxymethyl}-naphthalen-2-ylmethoxy)-ethanol.

31. The compound of claim 20 wherein said compound is 7-{(3R,4R)-4-[4-(3-benzyloxy-propoxy)-phenyl]-piperidin-3-yloxymethyl}-naphthalen-2-ylmethyl)-dimethyl-amine.

32. The compound of claim 16 wherein R^{102}, R^{103} and R^{105} are hydrogen.

33. The compound of claim 16 wherein all of R^{102}, R^{103}, R^{104} and R^{105} are hydrogen.

34. The compound of claim 33 wherein said compound is (3RS,4RS)-4-[4-(3-benzyloxy-propoxy)-phenyl]-3-(naphthalen-2-ylmethoxy)-piperidine.

35. The compound of claim 10 wherein R^4 is hydroxy, lower alkyl hydroxy, lower alkyl-lower alkoxy, 2-oxo-lower-imidazolidin-1-yl-lower-alkyl, amino-lower-alkyl-amino-lower-alkyl, 4-methyl-piperazin-1-yl-lower-alkoxy, 4-methyl-piperazin-1-yl-lower-alkyl-carbamoyloxy-lower-alkyl, hydroxy-lower-alkyl-oxy, morpholin-4-yl-lower-alkoxy, di-lower-alkyl-amino-lower-alkyl-amino-lower-alkyl, di-lower-alkyl-amino-lower-alkyl, pyridylthio-lower-alkyl, 1,2,4-triazolyl-lower-alkyl and tetrazolyl-lower-alkyl.

36. The compound of claim 35 wherein two of R^{102}, R^{103}, R^{104} and R^{105} are hydrogen.

37. The compound of claim 36 wherein R^{103} and R^{105} are hydrogen.

38. The compound of claim 37 wherein R^{102} and R^{104} are lower alkoxy.

39. The compound of claim 38 wherein R^4 is hydroxy.

40. The compound of claim 39 wherein said compound is (3R,4S,5S)-4-[4-(3-benzyloxy-propoxy)-phenyl]-3-(1,4-dimethoxy-naphthalen-2-ylmethoxy)-piperidin-5-ol.

42. The compound of claim 36 wherein three of R^{102}, R^{103}, R^{104} and R^{105} are hydrogen.

43. The compound of claim 42 wherein R^{102}, R^{104} and R^{105} are hydrogen.

44. The compound of claim 43 wherein R^{103} is N-methyl piperazino-N-lower alkoxy.

45. The compound of claim 44 wherein R^4 is hydroxy.

46. The compound of claim 45 wherein said compound is 1-[2-[7-[(3R,4S,5S)-5-hydroxy-4-[4-[-3-(2-methoxy-benzyloxy)-propoxy]-piperidin-3-yloxymethyl]-naphthalin-2-yloxy]-ethyl]-4-methyl-piperazine.

47. The compound of claim 42 wherein all of R^{102}, R^{103}, R^{104} and R^{105} are hydrogen.

48. The compound of claim 47 wherein said compound is 4-[(3R,4S,5S)-4-[4-(3-benzyloxy-propoxy)-phenyl]-3-(naphthalen-2-ylmethoxy)-piperidin-5-yloxy]-butan-1-ol.

49. The compound of claim 47 wherein said compound is 3-[(3R,4S,5S)-4-[4-(3-benzyloxy-propoxy)-phenyl]-3-(naphthalen-2-ylmethoxy)-piperidin-5-yloxy]-propan-1-ol.

50. The compound of claim 47 wherein said compound is 1-{2-[(3R,4R,5S)-4-[4-(3-benzyloxy-propoxy)-phenyl]-3-(naphthalen-2-ylmethoxy)-piperidin-5-yloxy]-ethyl}-4-methyl-piperazine.

51. The compound of claim 47 wherein said compound is 4-[2-(3R,4R,5S)-[4-[4(3-benzyloxy-propoxy)-phenyl]-3-(naphthalen-2-ylmethoxy)-piperidin-5-ylmethoxy]-ethyl]-morpholine.

52. The compound of claim 47 wherein said compound is (3S,4R,5R)-4-[2-[4-[4-(3-benzyloxy-propoxy)-phenyl]-5-(naphthalen-2-ylmethoxy)-piperidin-3-ylmethoxy]-ethyl]-morpholine.

53. The compound of claim 47 wherein said compound is (3S,4R,5R)-4-[4-(3-benzyloxy-propoxy)-phenyl]-3-methoxymethyl-5-(naphthalen-2-ylmethoxy)-piperidine.

54. The compound of claim 47 wherein said compound is (3S,4R,5R)-4-[4-(3-benzyloxy-propoxy)-phenyl]-5-(naphthalen-2-ylmethoxy)-piperidin-3-ylmethyl [3-(4-methyl-piperazin-1-yl)-propyl]-carbamate.

55. The compound of claim 47 wherein said compound is (3S,4R,5R)-4-[4-[4-(3-benzyloxy-propoxy)-phenyl]-5-(naphthalen-2-ylmethoxy)-piperidin-3-ylmethylsulphanyl]-pyridine.

56. The compound of claim 47 wherein said compound is (3S,4R,5R)-[4-[4-(3-benzyloxy-propoxy)-phenyl]-5-(naphthalen-2-ylmethoxy)-piperidin-3-yl]-methanol.

57. The compound of claim 47 wherein said compound is (3S,4R,5R)-N-[4-[4-(3-benzyloxy-propoxy)-phenyl]-5-(naphthalen-2-ylmethoxy)-piperidin-3-ylmethyl]-N,N',N'-trimethyl-ethane-1,2-diamine.

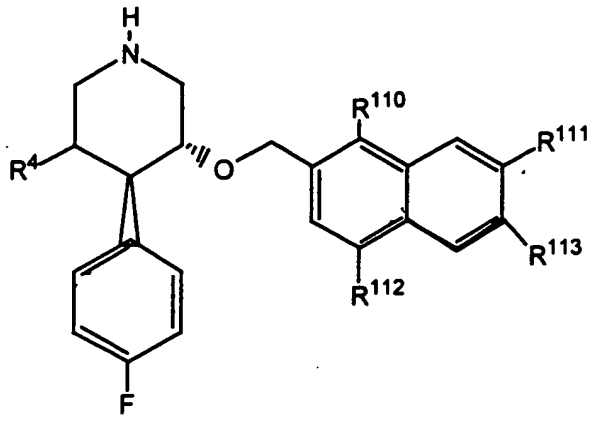
58. The compound of claim 47 wherein said compound is (3S,4R,5R)-[4-[4-(3-benzyloxy-propoxy)-phenyl]-5-(naphthalen-2-ylmethoxy)-piperidin-3-ylmethyl]-diethyl-amine.

59. The compound of claim 47 wherein said compound is (3R,4R,5S)-4-[4-(3-benzyloxy-propoxy)-phenyl]-3-(naphthalen-2-ylmethoxy)-5-[1,2,4]triazol-1-ylmethyl-piperidine.

60. The compound of claim 47 wherein said compound is (3S,4R,5R)-1-[4-[4-(3-benzyloxy-propoxy)-phenyl]-5-(naphthalen-2-ylmethoxy)-piperidin-3-ylmethyl]-imidazolidin-2-one.

61. The compound of claim 47 wherein said compound is (3R,4R,5S)-3-(1,4-dimethoxy-naphthalin-2-ylmethoxy)-4-{4-[3-(2-methoxy-benzyloxy)-propoxy]-phenyl}-5-(1H-tetrazol-5-ylmethyl)-piperidine.

62. The compound of claim 8 having the formula:



wherein R^4 is as in claim 1; R^{110}, R^{111}, R^{112} and R^{113} are independently hydrogen, lower alkoxy, hydroxy lower alkoxy, lower alkyl di-lower alkyl amino, 2,3-dihyroxypropoxy, 2,3-dihyroxypropoxy-lower alkyl, 2,3-dihyroxypropoxy-lower alkoxy, N-methyl piperazino-N-lower alkoxy, morpholino-lower-alkoxy, benzyloxy, and methoxy-benzyloxy.

63. The compound of claim 62 wherein R^{110}, R^{111} and R^{113} are hydrogen and R^{112} is benzyloxy.

64. The compound of claim 63 wherein R^4 is hydrogen or lower alkyl.

65. The compound of claim 64 wherein said compound is (3R,4R)-3-(4-benzyloxy-naphthalen-2-ylmethoxy)-4-(4-fluoro-phenyl)-piperidine.

66. The compound of claim 64 wherein said compound is (3S,4S)-3-(4-Benzyloxy-naphthalen-2-ylmethoxy)-4-(4-fluoro-phenyl)-piperidine.

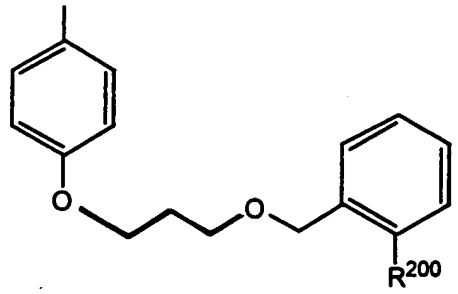
67. The compound of claim 64 wherein said compound is (3RS,4RS,5SR)-3-(4-Benzyloxy-naphthalen-2-ylmethoxy)-4-(4-fluoro-phenyl)-5-propyl-piperidine.

68. The compound of claim 5 wherein X is oxygen, Z is methyl, and R^1 is phenyl which is unsubstituted or substituted.

69. The compound of claim 68 wherein said phenyl is unsubstituted, or is 2,3-substituted by ethylene dioxy, or is substituted by one to three methoxy groups.

70. The compound of claim 69 wherein R^2 is para-substituted phenyl.

71. The compound of claim 70 wherein R^2 is a group of the formula:



wherein R^{200} is hydrogen or lower alkoxy.

72. The compound of claim 71 wherein R^4 is hydrogen.

73. The compound of claim 72 wherein said compound is (3RS,4RS)-4-[4-(3-Benzyloxy-propoxy)-phenyl]-3-(2,3-dihydro-benzo[1,4]dioxin-6-ylmethoxy)-piperidine.

74 The compound of claim 71 wherein R^4 is phenyl which is unsubstituted or substitued with from one to three methoxy groups.

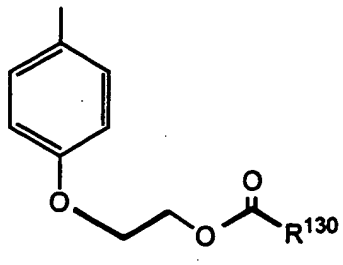
75. The compound of claim 74 wherein said compound is (3R,4s,5S)-4-[4-(3-benzyloxy-propoxy)-phenyl]-3,5-bis-(4-methoxy-benzyloxy)-piperidine.

76. The compound of claim 74 wherein said compound is (3R,4s,5S)-4-[4-(3-benzyloxy-propoxy)-phenyl]-3,5-bis-(3,4,5-trimethoxy-benzyloxy)-piperidine.

77. The compound of claim 71 wherein R^4 is hydroxyl.

78. The compound of claim 77 wherein said compound is (3R,4S,5S)-4-[4-(3-benzyloxy-propoxy)-phenyl]-3-(4-methoxy-benzyloxy)-piperidin-5-ol.

79. The compound of claim 8 wherein R^2 is a group of the formula:



wherein R^{130} is unsubstituted or substituted phenyl or unsubstituted or substituted thienyl.

80. The compound of claim 79 wherein R^1 is napthyl which is unsubstituted or substituted by benzyloxy wherein said benzene ring is substituted by methoxy or is unsubstituted.

81. The compound of claim 80 wherein R^{130} is phenyl which is substituted by chloro or is unsubstituted, or is unsubstituted thienyl.

82. The compound of claim 81 wherein R^4 is hydrogen, hydroxy, lower alkyl hydroxy, lower alkyl-lower alkoxy, 2-oxo-lower-imidazolidin-1-yl-lower-alkyl, amino-lower-alkyl-amino-lower-alkyl, 4-methyl-piperazin-1-yl-lower-alkoxy, 4-methyl-piperazin-1-yl-lower-alkyl-carbamoyloxy-lower-alkyl, hydroxy-lower-alkyl-oxy, morpholin-4-yl-lower-alkoxy, di-lower-alkyl-amino-lower-alkyl-amino-lower-alkyl, di-lower-alkyl-amino-lower-alkyl, or 1,2,4-triazolyl-lower-alkyl.

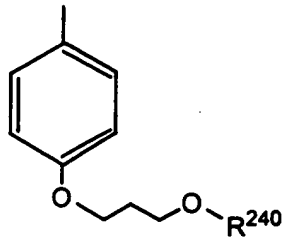
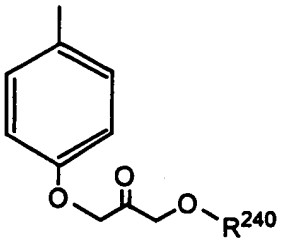
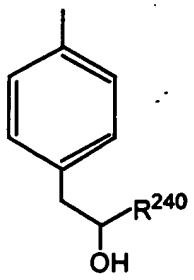
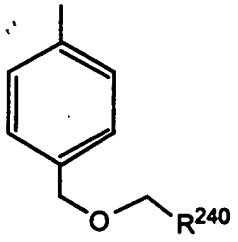
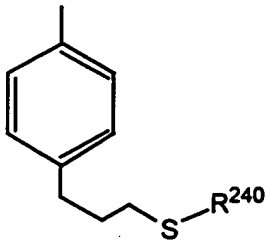
83. The compound of claim 82 wherein R^4 is hydrogen.

84. The compound of claim 83 wherein said compound is (3RS,4RS)-2-[4-(3-Naphthalen-2-ylmethoxy-piperidin-4-yl)-phenoxy]-ethyl 2-chloro-benzoate hydrochloride.

85. The compound of claim 83 wherein said compound is (3RS,4RS)-2-[4-[3-[4-(2-methoxy-benzyloxy)-naphthalen-2-ylmethoxy]-piperidin-4-yl]-phenoxy]-ethyl benzoate hydrochloride.

86. The compound of claim 83 wherein said compound is (3RS,4RS)-2-[4-(3-naphthalen-2-ylmethoxy-piperidin-4-yl)-phenoxy]-ethyl thiophene-2-carboxylate hydrochloride.

87. The compound of claim 8 wherein R^2 is a group of the formula:





or


wherein R^{240} is phenyl which may be substituted or unsubstituted.

88. The compound of claim 87 wherein R^1 is naphthyl which is unsubstitued or substituted by methoxy.

89. The compound of claim 88 wherein R^4 is hydrogen, hydroxy, lower alkyl hydroxy, lower alkyl-lower alkoxy, 2-oxo-lower-imidazolidin-1-yl-lower-alkyl, amino-lower-alkyl-amino-lower-alkyl, 4-methyl-piperazin-1-yl-lower-alkoxy, 4-methyl-piperazin-1-yl-lower-alkyl-carbamoyloxy-lower-alkyl, hydroxy-lower-alkyl-oxy, morpholin-4-yl-lower-alkoxy, di-lower-alkyl-amino-lower-alkyl-amino-lower-alkyl, di-lower-alkyl-amino-lower-alkyl, or 1,2,4-triazolyl-lower-alkyl.

90. The compound of claim 89 wherein R^4 is hydrogen or lower alkyl-lower alkoxy and R^{240} is unsubstituted phenyl or phenyl substituted with methoxy.

91. The compound of claim 90 wherein said compound is (3RS,4RS)-3-(Naphthalen-2-ylmethoxy)-4-[4-(3-phenylsulphanyl-propyl)-phenyl]-piperidine.

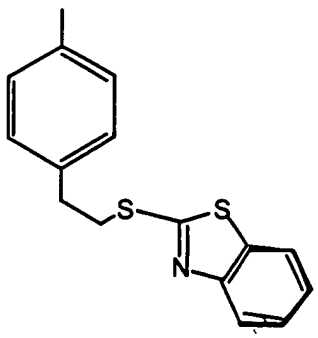
92. The compound of claim 90 wherein said compound is (3SR,4RS,5RS)-4-(4-Benzyloxymethyl-phenyl)-3-methoxymethyl-5-(naphthalen-2-ylmethoxy)-piperidine.

93. The compound of claim 90 wherein said compound is (3RS,4RS)-3-(naphthalen-2-ylmethoxy)-4-[4-(3-phenyl-isoxazol-5-ylmethoxy)-phenyl]-piperidine trifluoroacetate.

94. The compound of claim 90 wherein said compound is (3RS,4RS)-3-(Naphthalen-2-ylmethoxy)-4-[4-(3-phenyl-[1,2,4]oxadiazol-5-ylmethoxy)-phenyl]-piperidine trifluoroacetate.

95. The compound of claim 90 wherein said compound is (3R,4R)-3-(1,4-dimethoxy-naphthalen-2-ylmethoxy)-4-[4-[3-(2-methoxy-phenoxy)-propoxy]-phenyl]-piperidine.

96. The compound of claim 8 wherein R^2 is a group of the formula:



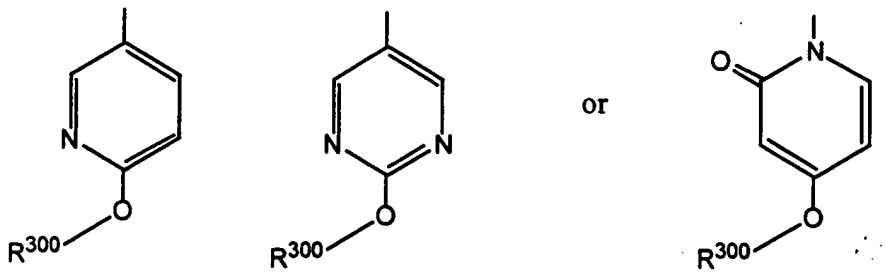
97. The compound of claim 96 wherein R^1 is naphthyl which is unsubstitued or substituted by hydroxy.

98. The compound of claim 97 wherein R^4 is hydrogen, hydroxy, lower alkyl hydroxy, lower alkyl-lower alkoxy, 2-oxo-lower-imidazolidin-1-yl-lower-alkyl, amino-lower-alkyl-amino-lower-alkyl, 4-methyl-piperazin-1-yl-lower-alkoxy, 4-methyl-piperazin-1-yl-lower-alkyl-carbamoyloxy-lower-alkyl, hydroxy-lower-alkyl-oxy, morpholin-4-yl-lower-alkoxy, di-lower-alkyl-amino-lower-alkyl-amino-lower-alkyl, di-lower-alkyl-amino-lower-alkyl, or 1,2,4-triazolyl-lower-alkyl.

99. The compound of claim 98 wherein R^4 is hydrogen.

100. The compound of claim 99 wherein said compound is (3RS,4RS)-3-[4-[4-[2-(benzothiazol-2-ylsulphanyl)-ethyl]-phenyl]-piperidin-3-yloxymethyl]-naphthalen-1-ol.

101. The compound of claim 7 wherein R^2 is a group of the formula:



wherein R^{300} is lower alkoxy-benzyloxy in which the benzene is substituted by lower alkoxy or is unsubstituted, or lower alkyl-cycloalkyl.

102. The compound of claim 101 wherein R^3 and R^4 are hydrogen and R^1 is disubstituted by methoxy.

103. The compound of claim 102 wherein said compound is (3'R,4'R)-6-(3-cyclohexyl-propoxy)-3'-(1,4-dimethoxy-naphthalen-2-ylmethoxy)-1',2',3',4',5',6'-hexahydro-[3,4']bipyridine.

104. The compound of claim 102 wherein said compound is (3'R,4'R)-3'-(1,4-dimethoxy-naphthalen-2-ylmethoxy)-6-[3-(2-methoxybenzyloxy)-propoxy]-1',2',3',4',5',6'-hexahydro-[3,4']bipyridine.

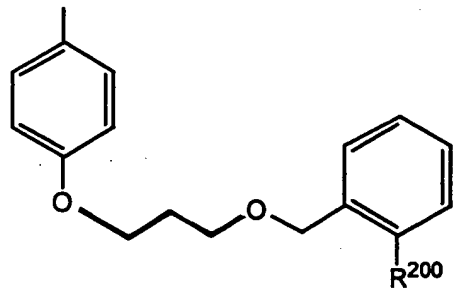
105. The compound of claim 102 wherein said compound is 2-(4-cyclohexyl-butoxy)-5-[(3R,4R)-3-(1,4-dimethoxy-naphthalen-2-ylmethoxy)-piperidin-4-yl]-pyrimidine.

106. The compound of claim 102 wherein said compound is (3'S,4'S)-3'-(1,4-dimethoxy-naphthalen-2-ylmethyoxy)-4-[S-(2-methoxy-benzyloxy)-propoxy]-1',2',3',4',5',6'-hexahydro-[1,4']bipyridin-2-one.

107. The compound of claim 5 wherein X is oxygen, Z is methylene, and R^1 is 6- or 7-quinolyl, 6- or 7-isoquinolyl, 6- or 7-tetrahydroquinolyl, 6- or 7-tetrahydro-isoquinolinyl, or R^1 is 6- or 7-tetrahydroquinolyl or 6- or 7-tetrahydroisoquinolyl substituted by oxo.

108. The compound of claim 107 wherein R^2 is para-substituted phenyl.

109. The compound of claim 108 wherein R^2 is a group of the formula:



wherein R^{200} is hydrogen or lower alkoxy.

110. The compound of claim 109 wherein R^3 and R^4 are hydrogen.

111. The compound of claim 110 wherein said compound is (3R,4R)-4-[4-[3-(2-methoxy-benzyloxy)-propoxy]-phenyl]-3-(quinolin-7-ylmethoxy)-piperidine.

112. The compound of claim 110 wherein said compound is (3R,4R)-3-(isoquinolin-7-ylmethoxy)-4-[4-[3-(2-methoxy-benzyloxy)-propoxy]-phenyl]-piperidine.

113. The compound of claim 110 wherein said compound is (3R,4R)-4-[4-[3-(2-methoxy-benzyloxy)-propoxy]-phenyl]-3-(1,2,3,4-tetrahydro-quinolin-7-ylmethoxy)-piperidine.

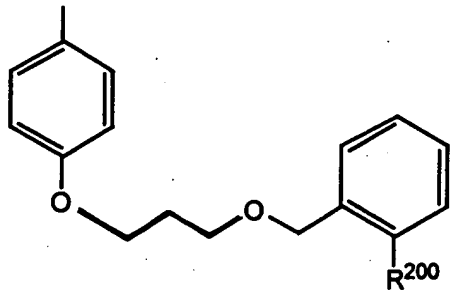
114. The compound of claim 110 wherein said compound is (3R,4R)-4-[4-[3-(2-methoxy-benzyloxy)-propoxy]-phenyl]-3-(2-oxo-1,2-dihydro-quinolin-7-ylmethoxy)-piperidine.

115. The compound of claim 5 wherein X is -CO- or -CHOR^9- wherein R^9 is acetyl, Z is methylene, and R^1 is naphthyl which is unsubstituted or substituted.

116. The compound of claim 115 wherein R^1 is napthyl which is unsubstituted or substituted by methoxy, hydroxy, benzyloxy wherein said benzene ring is substituted by methoxy or is unsubstituted, ethoxy morpholino, ethoxy piperidinyl wherein the second nitrogen atom is substituted by methyl or is unsubstituted, dihyroxypropoxy, ethoxy dihydroxypropoxy, methyl dihydroxypropoxy, methyl hydroxypropoxy, methyl hydroxyethoxy, or methy N,N-dimethyl amine.

117. The compound of claim 116 wherein R^2 is para-substituted phenyl.

118. The compound of claim 117 wherein R^2 is a group of the formula:



wherein R^{200} is hydrogen or lower alkoxy.

119. The compound of claim 118 wherein X is -CO-.

120. The compound of claim 119 wherein R^3 and R^4 are hydrogen.

121. The compound of claim 120 wherein said compound is 1-[(3R,4S-4-[4-(3-benzyloxy-propoxy)-phenyl]-piperidin-3-yl]-2-naphthalen-2-yl-ethanone.

122. The compound of claim 119 wherein R^3 is hydrogen and R^4 is morpholin-4-yl-lower-alkoxy-lower-alkyl.

123. The compound of claim 122 wherein said compound is 1-[(3R,4S,5S)-4-[4-(3-benzyloxy-propoxy)-phenyl]-5-(2-morpholin-4-yl-ethoxymethyl)-piperidin-3-yl]-2-naphthalen-2-yl-ethanone.

124. The compound of claim 117 wherein R^2 is p-fluorophenyl.

125. The compound of claim 124 wherein X is -CHOR^9- and R^3 and R^4 are hydrogen.

126. The compound of claim 125 wherein R^9 is benzoyl.

127. The compound of claim 126 wherein said compound is (SR)- or (RS)-1-[(3RS,4SR)-4-(4-fluoro-phenyl)-piperidin-3-yl]-2-naphthalen-2-yl-ethyl benzoate hydrochloride.

128. The compound of claim 1 wherein R^3 is hydrogen, m is 0 and R^2 is phenyl, pyridyl, pyrimidinyl, pyrazinyl or triazolyl which are unsubstituted or para-substituted, Q is ethylene, X is oxygen, -CO- or -CHOR^9- wherein R^9 is acetyl, n is 1 and Z is lower alkylene.

129. The compound of claim 128 wherein X is oxygen, Z is methylene, and R^1 is naphthyl which is unsubstituted or substituted.

130. The compound of claim 129 wherein R^1 is napthyl which is unsubstituted or substituted by methoxy, hydroxy, benzyloxy wherein said benzene ring is substituted by methoxy or is unsubstituted, ethoxy morpholino, ethoxy piperidinyl wherein the second nitrogen atom is substituted by methyl or is unsubstituted, dihyroxy propoxy, ethoxy dihydroxy propoxy, methyl dihydroxy propoxy, methyl hydroxy propoxy, methyl hydroxy ethoxy, or methy N,N-dimethyl amine.

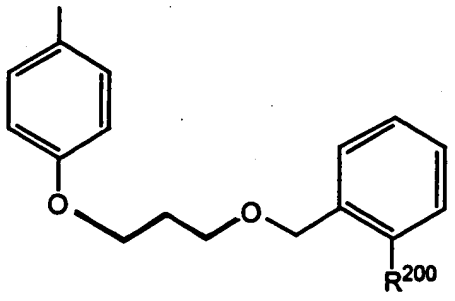
131. The compound of claim 130 wherein R^2 is para-substituted phenyl.

132. The compound of claim 131 wherein R^2 is p-fluorophenyl.

133. The compound of claim 132 wherein R^3 and R^4 are hydrogen.

134. The compound of claim 133 wherein said compound is (1RS,2RS,3RS,5SR)-2-(4-Benzyloxy-naphthalen-2-ylmethoxy)-3-(4-fluoro-phenyl)-8-aza-bicyclo[3.2.1]octane.

135. The compound of claim 131 wherein R^2 is a group of the formula:



wherein R^{200} is hydrogen or lower alkoxy.

136. The compound of claim 135 wherein R^3 and R^4 are hydrogen.

137. The compound of claim 39 which is (3R,4S,5S)-3-(1,4-dimethoxy-naphthalen-2-ylmethoxy)-4-[4-[3-(2-methoxy-benzyloxy)-propoxy]-phenyl]-piperidin-5-ol.